REMARKS/ARGUMENTS

Reconsideration and continued examination of the above-identified application are respectfully requested.

By way of this amendment, claims 1, 20, 21, and 28 have been amended. Support for the amendments can be found at least on page 18, lines 1-8 of the specification and page 64, lines 21-25. Applicants have also amended the Brief Description of the Drawings to refer to Sequence ID numbers as appropriate. The non-elected claims have been designated as withdrawn. Accordingly, no questions of new matter should arise and entry of the amendment is respectfully requested.

Objection to Specification

At page 3 of the Office Action, the Examiner states that the specification does not provide sequence identifiers for the two peptide sequences disclosed in Figure 1 and wants a trademark capitalized. In order to overcome this objection, Applicants have amended the Sequence Listing to include the two sequences referred to in Figure 1 and the Brief Description of the Drawings to refer to Sequence ID numbers as appropriate. Also, page 33 has been amended to capitalize Minisart ™. Accordingly, the Applicants respectfully request the Examiner to withdraw this objection.

Rejection of claims 1-9, 20-24, and 28 under 35 U.S.C. §112, second paragraph

At page 4 of the Office Action, the Examiner states that claims 1-9, 20-24, and 28 are rejected under 35 U.S.C. §112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The Examiner states that claims 1-9, 20-24, and 28 are indefinite because the claims recite that the antibody "carries" or "is carrying" a labeling substance in the linker part in claims 1 and 21. The Examiner

states that the terms "carries" and "is carrying" do not clearly describe the structural relationship between the labeling substance and the linker part of the antibody. In particular, the Examiner suggests that the claim language does not indicate whether the two molecules are attached, whether there is a dissociable reaction or a conjugate, and what sort of association or biochemical interaction is meant by the term "carrying." The Examiner further states that claims 9 and 28 are indefinite because the claims state that the antibody "has a Kd value that is equivalent to a Kd value of a naturally occurring antibody." The Examiner states that it is not clear what reference antibody is being used for comparison and whether the "naturally occurring antibody" is the parental or wild-type antibody of the single chain antibody. This rejection is respectfully traversed.

In order to assist the Examiner, Applicants have removed the terms "carries" and "is carrying" from the claims. The claims, as currently amended, specify that the linker is bound to a labeling substance. As provided at least on page 18, lines 1-8 of the specification, a labeling substance, such as biotin, can be bound to the linker part of an antibody.

The term "naturally occurring antibody," as used in claims 9 and 28, refers to the parental antibody of the single chain antibody. As discussed on page 64, lines 21-25 of the specification, for example, the single chain antibody that was prepared in Example 1 has a Kd value equivalent to that of complete anti-Salmonella antibody IgG. In order to further assist the Examiner, Applicants have replaced the phrase "naturally occurring antibody" with the phrase "parental antibody." Accordingly, these rejections should be withdrawn.

Rejection of claims 1 and 2 under 35 U.S.C. §102(b) -- Luo et al.

At page 5 of the Office Action, the Examiner states that claims 1 and 2 are rejected under 35 U.S.C. §102(b) as being anticipated by Luo et al. (J. BIOTECHNOL. 65:225-228 (1998)). The

Examiner states that claims 1 and 2 are drawn to a single chain antibody comprising a linker where the linker comprises a labeling substance. The Examiner further states that the claims do not limit where the linker should occur within the structure of the single chain antibody or how the linker relates structurally or functionally to the labeling substance. The Examiner states that Luo discloses a scFv with a C-terminal extension comprising a biotin mimetic sequence (BMS) or c-Myc-BMS or c-Myc-BMS for use as an in vitro diagnostic. The Examiner states that the BMS is disclosed as having a high affinity for streptavidin (p. 226, col. 2, para. 3). This rejection is respectfully traversed.

Applicants have amended claim 1 to specify that the heavy chain and the light chain of the single chain antibody are cross-linked through a linker and that the linker is bound to a labeling substance. Applicants respectfully submit that Luo et al. does not teach or suggest a single-chain antibody having a linker which cross-links a heavy chain and a light chain and which is bound to a labeling substance. Accordingly, this rejection should be withdrawn.

Rejection of claims 1 and 2 under 35 U.S.C. §102(b) -- Schultz et al.

At the top of page 6 of the Office Action, the Examiner states that claims 1 and 2 are rejected under 35 U.S.C. §102(b) as being anticipated by Schultz et al. (CANCER RES. 60:6663-6669). The Examiner states that Schultz et al. discloses a scFvSA construct where the scFv comprises Vh and Vl domains from the anti-CD20 antibody fused to the full length streptavidin. The Examiner states that the linker sequences are interposed between the Vh and Vl domains, and between the VI and SA domains as shown in Figure 2. The Examiner further states that Schultz et al. discloses the SA domain as a label for binding to biotin. This rejection is respectfully traversed.

Unlike the present claims, Schultz et al. does not teach or suggest a linker, which crosslinks

a heavy chain and a light chain, and which is also bound to a labeling substance. Thus, Schultz et al. does not anticipate the present claims. Accordingly, this rejection should be withdrawn.

Rejection of claims 1-8 under 35 U.S.C. §102(b) -- Mascarenhas et al.

Beginning at page 6 of the Office Action and continuing to page 7, the Examiner states that claims 1-8 are rejected under 35 U.S.C. § 102(b) as being anticipated by Mascarenhas et al. (U.S. Patent No. 5,914,254). It appears that the Examiner has construed claims 3-8 as being drawn to an antibody of heavy and light chains or variable regions carrying a labeling substance in the linker, wherein the labeling substance binds to a polypeptide of the linker in the presence of an enzyme (claims 3 and 4) or wherein the labeling substance is incorporated into the linker (claims 5 and 6) or wherein the labeling substance is biotin and the enzyme is biotin ligase (claims 7 and 8). The Examiner states that Mascarenhas et al. discloses fusion proteins comprising single chain antibodies having linker peptides inserted between the VH and VL domains. According to the Examiner, Mascarenhas et al. discloses that the linker peptides can serve as an "affinity tag" to aid in the purification of the fusion polypeptide away from other cellular polypeptides, for example, multiple histidine residues, or can comprise a biotinylation sequence which is recognized by biotin holoenzyme synthetase. This rejection is respectfully traversed.

Contrary to the Examiner's suggestion, Applicants note that Mascarenhas et al. only discusses linker peptides which are positioned between the fusion partner and the peptide of interest (col. 13, lines 17-64). Applicants point out that Mascarenhas et al. does not make mention of a linker which cross-links the heavy chain and the light chain of an antibody and which is a bound to a labeling substance, as recited in the present claims. Accordingly, Mascarenhas et al. does not anticipate the present claims. As such, this rejection should be wtihdrawn.

Rejection of claims 1-9, 20-24, and 28 under 35 U.S.C. §102(e) -- Fricker et al.

At page 7 of the Office Action, the Examiner states that claims 1-9, 20-24, and 28 are rejected under 35 U.S.C. §102(e) as being anticipated by Fricker et al. (U.S. Patent Application Publication No. 2004/0265902). The Examiner states that claim 9 is drawn to an antibody of heavy and light chains or variable regions carrying a labeling substance in the linker, where the antibody has a Kd similar to a naturally occurring antibody produced by wheat embryo cell-free translation system. The Examiner states that claims 20-23 are drawn to methods for immobilizing the single chain antibodies of the invention by reaction with a binding substance recognized by the labeling substance. The Examiner states that claims 24 and 28 are drawn to immobilized single chain antibodies having a Kd similar to a naturally occurring antibody produced by wheat embryo cell free translation system. The Examiner states that Fricker discloses a probe comprising an "idiotype network." According to the Examiner, the "idiotype network" comprises i) a target binding site moiety (e.g., idiotype scFv) which is attached to a first fluorescent polypeptide; ii) a mimic moiety (e.g., anti-idiotype scFv) which is capable of binding to the target binding site moiety and which is attached to a second fluorescent polypeptide; and (iii) a linker which connects the two fluorescent polypeptides, where the linker comprises one or more of : (1) a sequence capable of being recognized and bound by an immobilized component; (2) a protease cleavage site; (3) a non-analyte binding site; (4) two or more copies of the sequence (SerGly.sub.3); or (5) one or more copies of a rod domain from a structural protein (para. 0122). The Examiner states that Fricker discloses probes comprising a biotinylation peptide sequence, where for example, the mimic moiety comprises such a sequence (para. 0057). According to the Examiner, Fricker discloses that biotinylated probes are produced by a 17 residue biotin acceptor sequence that acts as a substrate for biotin ligase and permits the creation of endogenously biotinylated proteins (para. 0059). The

Examiner further states that Fricker discloses a peptide sequence capable of being recognized and bound by an immobilized component such as a hexa-histidine tag (His_6), an antibody epitope, or a sequence recognized by a protein modification enzyme (for example, a biotinylation site, glycosylation site or a phosphoryaltion site) (para. 0081). According to the Examiner, Fricker also discloses producing the probes in cell-free translation systems (para. 0055), including wheat (0158). The Examiner states that the probe for an "idiotypic network" in Fricker reads on and anticipates the present claims because, the Examiner alleges, the present claims do not specify that the heavy and light chain domains for the single-chain antibody is directly cross-linked through the linker and because the claims do not exclude other components, such as first and second fluorescent proteins as being part of the single chain antibody. This rejection is respectfully traversed.

It appears that the Examiner is suggesting that the "mimic moiety" and the "target binding site moiety" in Fricker correspond with the heavy and light chains of the present invention. However, the "target binding site moiety" is attached to one fluorescent polypeptide and that the "mimic moiety" is attached to another fluorescent polypeptide. Unlike the present invention, the linker in Fricker attaches to the two fluorescent polypeptides. Fricker does not teach or suggest a linker that directly cross-links heavy and light chain domains, as recited in the present claims. Accordingly, this rejection should be withdrawn.

Rejection of claims 1-9, 20-24, and 28 under 35 U.S.C. §103(a) -- Mascarenhas et al. in view of Fricker et al.

At page 9 of the Office Action, the Examiner states that claims 1-9, 20-24, and 28 are rejected under 35 U.S.C. §103 (a) as being unpatentable over Mascarenhas et al. (U.S. Patent No. 5,914,254) in view of Fricker et al. (U.S. Patent Application Publication No. 2004/0265902). The Examiner acknowledges that Mascarenhas does not teach expression of the single chain antibodies

in cell-free systems such as wheat or a method of making immobilized antibodies or immunobilized antibodies. The Examiner states that both Mascarenhas and Fricker teach single chain antibodies which are fusion proteins having peptide linkers or spacers which further comprise or have inserted within the spacer/linker a labeling molecule such as a polyhistidine tag or biotinylation peptide sequence. The Examiner states that each of the references recognizes the biotin/biotin ligase reaction for producing a biotin label for further interaction with a streptavidin substrate, and that Fricker extends this to methods for immobilization of the antibody to produce immobilized antibodies. The Examiner states that Fricker discloses cell-free translation of the antibodies and expression in wheat. The Examiner also states that because Fricker discloses producing a multimeric scFv complex under these conditions, one skilled in the art could have readily modified the scFv of Mascarenhas to include His tag labels inserted within the peptide linker in order to arrive at the instant claimed single chain antibodies, immobilization methods and immobilized forms thereof. The Examiner reasons that because the scFv of Mascarehnhas is a simplification of the "idiotype network" of Fricker, one would have been further motivated to have combined the references and been assured of success in doing so to produce immobilized forms of the antibodies and expressed in wheat embryo translation systems. This rejection is respectfully traversed.

Mascarenhas does not make mention of a linker which cross-links the heavy chain and the light chain of an antibody and which is bound to a labeling substance, as recited in the present claims. Mascarenhas only discusses linker peptides which are positioned between the fusion partner and the peptide of interest (col. 13, lines 17-64). Thus, it would not have been obvious to modify the scFv of Mascarenhas to include His tag labels inserted within a peptide linker which cross-links the heavy chain and the light chain of an antibody, as suggested by the Examiner.

Applicants also point out that none of the cited references describe that if the linker moiety

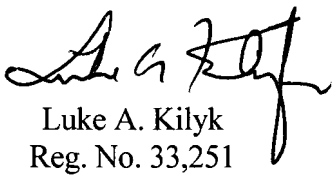
of a single chain antibody is loaded with a labeling material, it can be labeled without affecting its ability to recognize antigens. Such a concept is not considered to be obvious to a person skilled in the art either. In this regard, it was clarified that the single chain antibody prepared in Example 1 and immobilized by binding between biotin and streptavidin has a Kd value equivalent to that of complete IgG antibody. *See* Table 1 of the present application. Accordingly, this rejection should be withdrawn.

CONCLUSION

In view of the foregoing remarks, the applicant respectfully requests the reconsideration of this application and the timely allowance of the pending claims.

If there are any fees due in connection with the filing of this response, please charge the fees to our Deposit Account No. 50-0925. If a fee is required for an extension of time under 37 C.F.R. § 1.136 not accounted for above, such extension is requested and should also be charged to said Deposit Account.

Respectfully submitted,



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